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(71) Applicant *(for all designated States except US)*: BOMAC LABORATORIES LIMITED [NZ/NZ]; Corner Wiri Station Road and Hobill Avenue, Manukau City, Auckland (NZ).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: McLAREN, Donald, George [NZ/NZ]; Whitford Road, R D 1, Howick, Auckland (NZ). LEECH, Wayne, Frederick [NZ/NZ]; 2/6 Waikato Place, St. Johns, Auckland (NZ).

(74) Agents: BENNETT, Michael, R. et al.; A. J. Park & Son, Huddart Parker Building, 6th floor, Post Office Square, P.O. Box 949, Wellington 6015 (NZ).

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(54) Title: ANTHELMINTIC PREPARATION

(57) Abstract

A pour-on anthelmintic composition, including its method of preparation and use, the composition preferably having been prepared by mixing at a common temperature (i) a premix of an anthelmintic compound or compounds (for example a benzimidazole) with a transdermal vehicle (such as isopropyl myristate) with (ii) a premix of a non-ionic emulsifier with an oil capeble of solubilising the emulsifier and, subsequent to the blending of the premixes (preferably after cooling), mixing the blend with a deflocculation agent/diluent or deflocculation agent/diluent mix.

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"ANTHELMINTIC PREPARATION"

TECHNICAL FIELD

This invention relates to a method of preparing an anthelmintic composition and/or an anthelmintic composition (including a preparation so prepared) and/or a method of using such a composition.

BACKGROUND ART

Benzimidazole anthelmintics are widely used orally in aqueous suspension formulations for the control of parasitic helminths, namely round worms (nematodes), tapeworms (cestodes), or flukes (trematode). This anthelmintic group has been used in a variety of animal species including sheep, cattle, goats, deer, horses, cats, dogs, llama buffalo and poultry. Injectable preparations of benzimidazole anthelmintics are also known. Benzimidazole anthelmintic compounds are widely used in veterinary medicine. Common forms include oxfendazole, mebendazole, fenbendazole, albendazole and the probenzimidazoles febantel and netobimin, which are metabolised to benzimidazoles within the animal.

In general, these compounds are sparingly soluble in aqueous solutions although the solubility can be improved by heating the aqueous solution.

Bayer AG British Patent Specification No.1527584, the full content of which is hereby included by way of reference, refers to the advantages of pour-on application in veterinary practice over oral treatments and additionally discloses a pour-on formulation characterised in that the active compound is dissolved, emulsified or suspended in a suitable solvent or solvent mixture which is tolerable by the skin (optionally with addition of further auxiliaries) and applied with the aid of a suitable device, eg. measuring cup or spray bottle to the skin of the animal to be treated. The active ingredients disclosed are Tetramisole and Levamisole.

Reference should also be had to the paper "Seasonal Variation and Anthelmintic Response by Cattle to dermally applied Levamisole", B.A. Forsyth et al. Australian Veterinary Journal, Vol. 60 No.5, May 1983 and "Pharmacokinetics of ivermectin after oral or percutaneous administration to adult milking goats", E.W. Scott et al., Journal

Veterinary Pharmacology, Volume 13, pages 432-435, 1990.

E.R. Squibb & Sons Inc, US Patent Specification No.4145433 discloses the option of topical or parenteral administration to mammalian hosts of benzimidazole dispersed in a non-toxic, non-pyrogenic acceptable carrier. In particular it discloses a solution for cutaneous administration being prepared by dissolving 327 mg of [5-(benzyl)sulfinyl]-1H-benzimidazole-2-yl] carbamic acid, methyl ester in a solution of about 4cc xylene and 1cc dimethyl sulfoxide. Such administrations are stated as being useful in treating infection caused by Haemonchus, Ostertagia, Trichostrongylus, Cooperia, Dictyocaulus, Nematodirus, Bunostomum, Strongyloides, Oesphagostomum, Trichuris and liver flukes at a recommended dosage of from 2.5-25 mg/kg body weight.

DISCLOSURE OF INVENTION

Nevertheless the sparing solubility of anthelmintics restricts their use as pour-ons.

The present invention relates to improved methods of formulating compositions of anthelmintics (preferably benzimidazoles) for topical or transdermal administration to provide a substantially stable composition despite any solubility difficulties with the (benzimidazole) active ingredient(s).

It is an object of the present invention to provide a method of preparing an alternative anthelmintic composition and/or an anthelmintic composition and/or a method of using an anthelmintic composition which will obviate or minimise the foregoing disadvantages in a simple yet effective manner or which will at least provide the public with a useful choice. More specifically, it is an object of the present invention to provide alternative veterinary preparations, and/or methods of preparation and/or of use of veterinary preparations, whereby preferably benzimidazole anthelmintics may be applied externally to animals so as to pass into and/or through the skin and into the system(s) [eg. blood, lymph and/or tissue] of the animal, providing a simple and quick administration method which is effective in achieving the necessary dose response.

In addition it may provide a simple more prolonged method of administering the anthelmintic, increasing the anthelmintics effectiveness.

Accordingly in one aspect the invention consists in a method of preparing an anthelmintic composition capable by means of dermal application of delivery of a

effective anthelmintic amount one or more active ingredients into an animal systemically, said method comprising:

(i) mixing at least one anthelmintic compound with a vehicle in which said compound(s) dissolves, suspends and/or emulsifies until the vehicle/active ingredient mixture is substantially homogeneous,

(ii) before, simultaneously with, or after step (i), mixing a non-ionic emulsifier with an oil capable of solubilising the non-ionic emulsifier, said mixing being at a temperature where both the non-ionic emulsifier and oil are in a liquid phase,

(iii) blending the mixtures of steps (i) and (ii) at a temperature at which all components are in the liquid phase so as to provide a substantially homogeneous mixture,

(iv) lowering the temperature, or allowing the lowering of the temperature, of the mixture of step (iii) while mixing (preferably so that at least said non-ionic emulsifier is no longer in the liquid phase), and

(v) mixing with the suspension of step (iv) a deflocculation agent/water (or other diluent) mixture to provide the anthelmintic micro suspension preparation.

Preferably said anthelmintic active ingredient is at least one benzimidazole or prodrug therefor.

Other options include an avermectin, pyrantel, morantel, closantel, praziquantel etc.

Preferably said benzimidazole(s) or prodrug thereof is selected from the group including oxfendazole, thiabendazole, albendazole, cambenazole, fenbendazole, flubendazole, mebendazole, oxibendazole, parbendazole, thiophanate, febantel and netobimin.

Preferably said benzimidazole(s) is or are oxfendazole and/or albendazole.

Preferably said benzimidazole(s) is oxfendazole.

Preferably said vehicle is selected from the group including isopropyl myristate, dimethyl sulphoxide, diacetone alcohol, n-methyl-2-pyrrolidone, iso-propyl alcohol, dimethylforamide, and 2 pyrrolidone.

Preferably said vehicle is isopropyl myristate.

In addition to said vehicle a cosolvent and/or absorption enhancer is selected from the group including polyoxyethylen glyceroltriricinoleate, polyvinylpyrrolidone,

polyoxyethylene - glycerol trihydroxystearate, dimethylformamide (DMF), dimethyl-acetamide, dimethyl isosorbide.

Preferably the mixture of step (i) is elevated in temperature prior to the blending step (iii).

Preferably the temperature of blending step (iii) is from about 55°C to about 60°C.

Preferably the oil of step (ii) capable of solubilising the non-ionic emulsifier is a mineral oil or a vegetable oil.

Preferably said oil is selected from the group consisting of rapeseed or canola oil, polyol fatty acid ester, lauric acid hexyl, oleic acid decyl ester, 2-octyl dodecanol, soybean, sunflower oil, and ground nut refined fixed oils.

Preferably said non-ionic emulsifier of step (ii) is selected from the group including sorbitan stearate, polysorbates [including ethoxy (20) sorbitan monopalmitate, ethoxy (20) sorbitan monostearate, ethoxy (4) sorbitan monostearate and ethoxy (20) sorbitan tristearate], polyoxyethylene castor oils and polyoxyethylene glycols.

Preferably said non-ionic emulsifier of step (ii) is sorbitan stearate.

Preferably the step (ii) is carried out at an elevated temperature.

Preferably said elevated temperature at which step (ii) is carried out is from about 55°C to about 60°C.

Preferably the blending step (iii) is carried out only after the substantially homogeneous mixture of step (i) has been raised to a temperature of from about 55°C to about 60°C.

Preferably the temperature lowering step (iv) is to room or ambient temperature(s).

Preferably the deflocculation agent/water mixture is of a deflocculation agent selected from the group consisting of sodium lignosulphonate, silicon dioxides, poly vinyl pyrrolidones and/or said diluent is water.

Preferably said deflocculation agent is sodium lignosulphonate.

Preferably said deflocculation agent/water mixture has been mixed with a sonic mixing procedure.

Preferably said deflocculation agent/water mixture is added to the mixture of step (iv) substantially at room or ambient temperatures.

Preferably the composition comprises -

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Sorbitan Stearate	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Canola Oil	0.5% w/v
Deionised Water	Up to the 100%.

Preferably said mixture includes at least one or more of the following compounds, a trace mineral or trace minerals, a synthetic pyrethroid or pyrethroids (eg; cypermethrin), an organic phosphate or organophosphates, closantel, pyrantel, morantel, praziquantel and synthetic pyrethroids.

Preferably any such optional trace mineral(s) organophosphate(s) and/or closantel sodium is mixed into

(a), in the case of trace mineral(s) the pre-mix of step (iv) or (v),

(b), in the case of any organophosphate(s), in a mix of step (iv) or (v),

(c) in the case of closantel sodium, a mix of step (i),

(d) in the case of pyrantel or morantel, a mix of step (i),

(e) in the case of praziquantel, a mix of step (i),

(f) in the case of synthetic pyrethroid(s), a mix of step (i).

In a further aspect the invention is a benzimidazole anthelmintic composition prepared by a method as previously defined.

In still a further aspect the invention consists in an anthelmintic composition capable of being used transdermally such as by a pour-on procedure, said composition comprising at room or ambient temperature

at least one benzimidazole or prodrug thereof dissolved in, suspended on and/or emulsified by a transdermal vehicle and a liquid carrier for such benzimidazole/vehicle which includes a non-ionic emulsifier, an oil which solubilises the non-ionic emulsifier, water or other suitable diluent and a deflocculation agent.

Preferably said composition comprises -

Benzimidazole(s)	1% to 50% w/v,
Transdermal vehicle(s)	2% to 80% w/v,
Non-ionic emulsifier(s)	0.1% to 10% w/v,

Oil(s)	0.1% to 10% w/v,
Deflocculation agent(s)	0.1% to 10%, and
Water or other suitable diluent	5% to 50% w/v.

Preferably said benzimidazole or prodrug thereof is selected from the group consisting of oxfendazole, thiabendazole, albendazole, cambenazole, fenbendazole, flubendazole, mebendazole, oxibendazole, parbendazole, thiophanate, febantel and netobimin,

said vehicle is selected from the group including isopropyl myristate, dimethyl sulphoxide, diacetone alcohol, n-methyl-2-pyrrolidone and 2 pyrrolidone,

said oil is selected from the group including rapeseed or canola oil, polyol fatty acid ester, lauric acid hexyl, oleic acid decyl ester, 2-octyl dodecanol, soybean, sunflower oil, cold pressed rapeseed and ground nut refined fixed oils.

said non-ionic emulsifier is selected from the group including sorbitan stearate, polysorbates, polyoxyethylene castor oils and polyoxyethylene glycols and

said deflocculation agent is selected from the group including sodium lignosulphonate, silicon dioxides, poly vinyl pyrrolidones.

Preferably said benzimidazole is oxfendazole, said vehicle is isopropyl myristate, said oil is rapeseed or canola oil, said non-ionic emulsifier is sorbitan stearate and said deflocculation agent is sodium lignosulphonate.

Preferably said composition comprises -

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Sorbitan Stearate	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Canola Oil	0.5% w/v
Deionised Water .	up to the 100%.

Preferably the composition additionally includes at least one trace mineral and/or at least one organo phosphate and/or closantel sodium.

In still a further aspect the invention consists in a method of controlling helminth(s) (nematode, cestode or trematode) within an animal which comprises applying to the skin of the animal an anthelmintic composition as herein defined and thereafter allowing at

least the anthelmintic compound(s) [preferably benzimidazole or prodrug compound(s)] to pass through and/or into the skin of the animal to enter the blood, lymph and/or tissue fluids of the animal in an anthelmintically effective amount.

Preferably said composition is applied by a pour-on procedure or other method of skin application.

Preferably said composition is about a 75mg/mL suspension of oxfendazole at about a dosage rate oxfendazole/weight of animal at least twice that recommended for oral administration currently being recommended for oxfendazole anthelmintic treatment of any such animal.

Preferably said composition is about a 75mg/mL suspension of oxfendazole at a dosage rate of about 10mg oxfendazole/kg body weight of the animal.

Preferably the animal is a ruminant but can be other mammals or even non mammals.

Preferably said veterinary preparation also includes a surface active dispersant or wetting agent.

In a further aspect the invention consists in an anthelmintic composition capable by dermal application to an animal of delivering an anthelminticly effective amount of systemic anthelmintic active ingredient into the animal,

systemic anthelmintic compound(s)	1% to 50% w/v,
emulsifier	0.1% to 10% w/v,
carrier solvent (transdermal vehicle)	2% to 80% w/v,
dispersant or wetting agent	0.1% to 10% w/v,
oil	0.1% to 10% w/v, and
diluent	5% to 50% w/v.

Preferably said anthelmintic compound is a benzimidazole.

BRIEF DESCRIPTION OF DRAWINGS

The invention also consists in methods of use thereof.

The present preferred forms of the invention will now be described. The accompanying drawing (Figure 1) is a plot of helminth egg counts against time.

BEST MODE(S) FOR CARRYING OUT THE INVENTION

According to the invention, a veterinary preparation is provided, along with a method of preparing a veterinary preparation, and a method of using a veterinary preparation.

The preparation is so formulated as to be suitable for dermal use, e.g. spread on, spray on, or pour-on (hereinafter "pour-on"). The invention is that the benzimidazole anthelmintic is presented in a carrier or solvent (hereafter "vehicle") which is capable of being absorbed through the skin. By preference, this vehicle is iso propyl myristate, although other compounds may be substituted, for example, dimethyl sulphoxide, diacetone alcohol, N-methyl-2-pyrrolidone, 2 pyrrolidone or other suitable non-toxic compounds which can be absorbed through the skin of the target animals. Thus the formulation when applied externally to the animal will pass through the skin and into the systems of the animal where it can take effect.

A typical formulation according to the invention consists of 1% to 50% w/v benzimidazole, 2% to 80% w/v vehicle, 5% to 50% w/v diluent, 0.1% to 10% w/v non-ionic emulsifier, 0.1% to 10% w/v deflocculant and 0.1% to 10% oily component.

The emulsifier in the preferred form of the invention is sorbitan stearate but this may be substituted by other non-ionic emulsifiers, for example, polysorbates, polyoxyethylene castor oils, polyoxyethylene glycols.

The dispersant or wetting agent is in the preferred form of the invention sodium lignosulphonate, but this may be substituted by silicon dioxides, poly vinyl pyrrolidones, or other surface active agents.

The preparation also contains an oily component. In the most presently preferred form of the invention, this is rapeseed oil but this may be substituted by polyol fatty acid ester, lauric acid hexyl, oleic acid decyl ester, 2-octyl dodecanol or other vegetable oils such as soybean or sunflower oil.

The preparation is made up to volume with a diluent, such as deionised water. This diluent may be substituted by or include or be (any one or more) other miscible diluents such as propylene glycol, sorbitol or glycerol.

Example

Oxfendazole	7.5% w/v

Iso Propyl Myristate	66.0% w/v
Sorbitan Stearate	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Rapeseed Oil	0.5% w/v
Deionised Water	Up to the 100%.

Other, anthelmintic or therapeutic substances may also be included in the preparation if desired, for example, minerals, trace elements, synthetic pyrethroids and organophosphates.

The composition of the present may be prepared as follows:

The benzimidazole anthelmintic, for example oxfendazole, is added to the carrier solvent, for example iso propyl myristate, and the two compounds are mixed until the mixture is thoroughly wetted.

The non-ionic emulsifier, for example sorbitan stearate is then added to the mixture while maintaining stirring, followed, while continuing to stir, by the dispersant or wetting agent, for example sodium lignosulphonate, and the suitable oily component, for example rapeseed or canola oil. The mixture is then made up to volume with the diluent, for example deionised water. The total mixture is then continued to be mixed until it is substantially homogeneous.

The more preferred procedure is

(i) mixing at least one anthelmintic compound (eg: oxfendazole) with a vehicle (eg: isopropyl myristate) in which said compound(s) dissolves, suspends and/or emulsifies until the vehicle/active ingredient mixture is substantially homogeneous,

(ii) before, simultaneously with, or after step (i), mixing a non-ionic emulsifier (eg: sorbitan stearate) with an oil (eg: rapeseed oil) capable of solubilising the non-ionic emulsifier, said mixing being at a temperature (preferably elevated to 55°C to 60°C) where both the non-ionic emulsifier and oil are in a liquid phase,

(iii) blending the mixtures of steps (i) and (ii) at a temperature (preferably elevated to 55°C to 60°C) at which all components are in the liquid phase so as to provide a substantially homogeneous mixture,

(iv) lowering the temperature, or allowing the lowering of the temperature, of the mixture of step (iii) (eg: to room or ambient temperature) while mixing so that at least said

non-ionic emulsifier is no longer in the liquid phase, and

(v) mixing with the suspension of step (iv) a deflocculation agent/diluent mixture (eg: sodium lignosulphate/water) to provide the anthelmintic micro suspension preparation, said diluent being selected from the group comprising water, propylene glycol, sorbitol and glycerol.

This procedure provides an anthelmintic composition which over time can provide most effective helminth control.

The following eleven formulations give examples of different formulations within the present invention.

FORMULATION 1

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Liposorb S	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Benzyl Alcohol	5.0% w/v
Deionised Water	qs to 100% v/v

FORMULATION 2

Albendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Liposorb S	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Benzyl Alcohol	5.0% w/v
Deionised Water	qs to 100% v/v

FORMULATION 3

Fenbendazole	2.5% - 10% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Liposorb S	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Benzyl Alcohol	5.0% w/v
Deionised Water	qs to 100% v/v

FORMULATION 4

Oxfendazole	7.5% w/v
Closantel - Sodium	2.5% w/v - 5.0% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Liposorb S	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Benzyl Alcohol	5.0% w/v
Deionised Water	qs to 100% v/v

FORMULATION 5

Praziquantel	2.5% w/v
Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Sodium Lignosulphonate	0.9% w/v
Liposorb S	1.0% w/v
Benzyl Alcohol	5.0% w/v
Deionised Water	qs to 100% v/v

FORMULATION 6

Oxfendazole	7.5% w/v
Cypermethrin	2.5% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Sodium Lignosulphonate	0.9% w/v
Benzyl Alcohol	5.0% w/v
Liposorb S	1.0% w/v
Deionised Water	qs to 100% v/v

FORMULATION 7

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Canola Oil	0.5% w/v
Sodium Lignosulphonate	0.9% w/v
Benzyl Alcohol	5.0% w/v
Liposorb S	1.0% w/v
Copper Disodium Ethylenediamine Tetra Acetate	10.7% w/v
Zinc EDTA	5.4% w/v
Cobalt EDTA	1.1% w/v
Sodium Selenate	0.57% w/v
EDDI	0.57% w/v
Deionised Water	qs to 100% v/v

FORMULATION 8

Benzimidazole(s)	1% - 20% w/v
Transdermal Vehicle(s)	2% - 80% w/v
Non-ionic Emulsifier(s)	0.1% - 10% w/v
Oil(s)	0.1% - 10% w/v
Deflocculation Agent(s)	0.1% - 10% w/v
Preservative(s)	0.5% - 10% w/v
Water or suitable diluent	1% - 50% v/v

FORMULATION 9

Benzimidazole(s)	1% - 20% w/v
Anthelmintic(s)	1% - 5% w/v
Transdermal Vehicle(s)	2% - 80% w/v
Non-ionic Emulsifier(s)	0.1 - 10% w/v
Oil(s)	0.1% - 10% w/v
Deflocculation Agent(s)	0.1% - 10% w/v
Preservative(s)	0.5% - 10% w/v
Water or other suitable diluent	1% - 50% v/v

FORMULATION 10

Benzimidazole(s)	1% - 20% w/v
Pyrethroid(s)	1% - 5% w/v
Transdermal Vehicle(s)	2% - 80% w/v
Non-ionic Emulsifier(s)	0.1% - 10% w/v
Oil(s)	0.1% - 10% w/v
Deflocculation Agent(s)	0.1% - 10% w/v
Preservative(s)	0.5% - 10% w/v
Water or other suitable dilutent	1% - 50% v/v

FORMULATION 11

Anthelmintic(s) (including Benzimidazole(s))	1% - 20% w/v
Transdermal Vehicle(s)	2% - 80% w/v
Non-ionic Emulsifier(s)	0.1% - 10% w/v
Oil(s)	0.1% - 10% w/v
Deflocculation Agent(s)	0.1% - 10% w/v
Trace Mineral(s)	1% - 25% w/v
Preservative(s)	0.5% - 10% w/v
Water or other suitable dilutent	1% - 50% v/v

This formulation may be administered to cattle, for example, in volume dosages of 35-45 mls for cattle of 250-310kg body weight. Of course veterinary advice should also be sought regarding dosages. Dosages in similar ratios are applicable to other animals, eg: sheep, goats, horses, deer, cats, dogs, camel, llama and buffalo.

Thus it can be seen that an improved benzimidazole anthelmintic preparation, a method of preparing a veterinary preparation, and a method of using a veterinary preparation are provided by the invention in its preferred form which have the advantage of increasing the convenience and effectiveness of use of such compounds, through providing for efficacious dermal application.

Thus the formulation when applied externally will pass into and/or through the skin and be transported by the blood, lymph or tissue fluids to act on the helminth (nematode, cestode or trematode) both within body tissues and body organs including muscle, lung, liver and kidney and within the lumen of both the gastrointestinal and respiratory tract.

The mechanism of action of the benzimidazole anthelmintics on helminths is believed to be due to their disruption of intracellular microtubular transport systems by binding selectively to and damage of, helminth tubulin, preventing tubulin polymerisation and the inhibition of microtubule formation. Benzimidazoles have also been shown to act at higher levels as inhibitors of metabolic enzymes, including malate dehydrogenase and fumarate reductase, and disrupt metabolic pathways within the helminth. Orally

Benzimadazoles appear to be most effective as anthelmintics (drenches) when given over several days rather than as an oral single dose.

The preparation may be applied may be applied according to the invention, dermally, eg. as a pour-on on to the mid line of the back or neck of animals such as cattle. The active ingredient (ie. the anthelmintic) is absorbed through the skin and into the blood, tissues and tissue fluids of the animal.

Data based on the application of the said pour on, in this case oxfendazole, at 2.2 times the oral dose rate (ie. 10mg/kg) produced blood serum levels up to 0.2μg/mL which is comparable with the blood levels seen in calves orally administered with oxfendazole at a dose rate of 4.5mg/kg. Blood oxfendazole levels in the said pour on calves were generally lower and unexpectedly persistent, with low levels of oxfendazole detected in their blood at day 3 and 4 after administration. Blood levels in calves that received oral oxfendazole were below detection (0.025μg/mL) at day 3.

A slower action was also seen in the reduction of faecal egg counts in the pour on group with significant reductions on day 2 and 3 after treatment compared with a significant reduction occurring at day 1 and 2 in the oral group (see Figure 1).

Figure 1 shows Faecal Egg Counts (F.E.C's) in Eggs per gram (EPG) in 6 month old Friesan Calves, treated with oral oxfendazole (Synanthic™) at a dose rate of 4.5 mg per kg, the trial oxfendazole pour-on at 10.0 mg/kg and untreated control animals. Treatment was at day 0.

The pour-on formulation used for these FEC/Time trials was

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Sorbitan Stearate	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Canola Oil	0.5% w/v
Deionised Water	Up to the 100%.

It has already been demonstrated that treatment regimes that provide more prolonged levels of benzimidazoles over a number of days such as appear to be demonstrated in this pour on product, increases the effectiveness of the anthelmintic.

Table 1 is a comparison of Faecal Egg Counts (F.e.c's) in 6 Month Old Friesan Calves Treated with Oral Oxfendazole (Synanthic™) At 4.5 Mg/Kg and Trial Pour Oxfendazole Product At 13.5 Mg/kg

TABLE 1

Oxfendazole Pour-on

Animal No	Treatment					
	Group	Day 1	Day 0	mean: -1,0	Day 7	Day 14
2	Control	-	0	0	0	100
5	Control	50	100	75	0	0
10	Control	100	200	150	100	300
12	Control	50	50	50	100	50
25	Control	500	300	400	200	400
33	Control	500	150	325	0	0
51	Control	200	0	100	450	300
58	Control	50	0	25	200	150
59	Control	450	400	425	400	600
70	Control	50	150	100	100	N.D.
geometric means		217	135	165	150	211
1	Oral	50	100	75	0	0
3	Oral	200	200	200	50	0
6	Oral	50	200	125	50	0
8	Oral	50	50	50	0	0
11	Oral	350	50	200	0	0
13	Oral	50	50	50	0	0
16	Oral	350	100	225	0	0
30	Oral	300	250	275	0	50
36	Oral	200	300	250	50	0
38	Oral	100	50	75	0	0
41	Oral	300	200	250	0	0
45	Oral	100	0	50	0	0
47	Oral	500	300	400	0	0
55	Oral	50	150	100	0	0
61	Oral	350	500	425	50	50

62	Oral	300	50	175	0	0
66	Oral	50	50	50	0	0
73	Oral	50	0	25	0	0
74	Oral	400	0	200	0	50
geometric mean		190	139	168	10	8
4	Pour-on	50	0	25	0	0
7	Pour-on	230	0	125	0	0
9	Pour-on	150	-	75	0	0
14	Pour-on	100	100	100	0	0
18	Pour-on	150	100	125	0	0
20	Pour-on	50	0	25	0	0
21	Pour-on	100	250	175	0	50
22	Pour-on	100	100	100	0	0
23	Pour-on	50	100	75	0	0
26	Pour-on	50	0	25	0	0
28	Pour-on	350	500	425	0	0
31	Pour-on	850	400	625	0	0
37	Pour-on	100	50	75	0	0
40	Pour-on	150	350	250	0	0
42	Pour-on	150	150	150	0	50
44	Pour-on	400	0	200	0	0
50	Pour-on	900	1550	1225	200	750
57	Pour-on	50	0	25	0	0
60	Pour-on	50	50	50	0	0
76	Pour-on	50	0	25	0	0
geometric mean		205	195	195	10	42

SUMMARY

Comparison of oral and pour-on formulations. Treatment groups are:

Group 0 = untreated controls,

Group 1 = oral drench, and

Group 3 = pour-on formulation

Note: All analyses were carried out on log-transformed FEC's.

The analysis of faecal egg counts (FEC's) shows that there were no significant differences between any of the groups either on day -1 or day 0. Subsequently, on days 7, 14 and 21 post-treatment there was a high significant difference between the untreated control group and the groups treated with oxfendazole (p <0.0001). There were no significant differences between the orally or topically treated groups.

CLAIMS

1. A method of preparing an anthelmintic composition capable by means of dermal application of delivery of a systemicly effective anthelmintic amount at least one active ingredient into an animal, said method comprising:

(i) mixing at least one anthelmintic compound with a vehicle in which said compound(s) dissolves, suspends and/or emulsifies until the vehicle/active ingredient mixture is substantially homogeneous,

(ii) before, simultaneously with, or after step (i), mixing a non-ionic emulsifier with an oil capable of solubilising the non-ionic emulsifier, said mixing being at a temperature where both the non-ionic emulsifier and oil are in a liquid phase,

(iii) blending the mixtures of steps (i) and (ii) at a temperature at which all components are in the liquid phase so as to provide a substantially homogeneous mixture,

(iv) lowering the temperature, or allowing the lowering of the temperature, of the mixture of step (iii) while mixing so that at least said non-ionic emulsifier is no longer in the liquid phase, and

(v) mixing with the suspension of step (iv) a deflocculation agent/diluent mixture to provide the anthelmintic micro suspension preparation, said diluent being selected from the group comprising water, propylene glycol, sorbitol and glycerol.

2. A method as claimed in claim 1 wherein said anthelmintic active ingredient is a benzimidazole or a prodrug thereof.

3. A method of claim 2 wherein said benzimidazole(s) is or are selected from the group including oxfendazole, thiabendazole, albendazole, cambenazole, fenbendazole, flubendazole, mebendazole, oxibendazole, parbendazole, thiophanate, febantel and netobimin.

4. A method as claimed in claim 3 wherein said benzimidazole(s) is oxfendazole.

5. A method of any one of claims 1 to 4 wherein said vehicle is selected from the group including isopropyl myristate, dimethyl sulphoxide, diacetone alcohol, n-methyl-2-pyrrolidone, dimethyl foramide and 2 pyrrolidone.

6. A method as claimed in claim 5 wherein said vehicle is isopropyl myristate.

7. A method as claimed in any one of the preceding claims wherein the mixture of step

(i) is elevated in temperature prior to the blending step (iii).

8. A method as claimed in claim 7 wherein the temperature of blending step (iii) is from about 55°C to about 60°C.

9. A method as claimed in any one of the preceding claims wherein the oil of step (ii) capable of solubilising the non-ionic emulsifier is a mineral oil or a vegetable oil.

10. A method as claimed in claim 9 wherein said oil is selected from the group including canola oil, rapeseed oil, polyol fatty acid ester, lauric acid hexyl, oleic acid decyl ester, 2-octyl dodecanol, soybean and sunflower oil.

11. A method as claimed in any one of the preceding claims wherein said non-ionic emulsifier of step (ii) is selected from the group including sorbitan stearate, polysorbates, [including ethoxy (20) sorbitan monopalmitate, ethoxy (20) sorbitan monostearate, ethoxy (4) sorbitan monostearate and ethoxy (20) sorbitan tristearate], polyoxyethylene castor oils and polyoxyethylene glycols.

12. A method as claimed in claim 11 wherein said non-ionic emulsifier of step (ii) is sorbitan stearate.

13. A method of any one of the preceding claims wherein the step (ii) is carried out at an elevated temperature.

14. A method as claimed in claim 13 wherein said elevated temperature at which step (ii) is carried out is from about 55°C to about 60°C.

15. A method as claimed in any one of the preceding claims wherein the blending step (iii) is carried out only after the substantially homogeneous mixture of step (i) has been raised to a temperature of from about 55°C to about 60°C.

16. A method as claimed in any one of the preceding claims wherein the temperature lowering step (iv) is to room or ambient temperature(s).

17. A method as claimed in any one of the preceding claims wherein the deflocculation agent/water mixture is of a deflocculation agent selected from the group including sodium lignosulphonate, silicon dioxides, poly vinyl pyrrolidones and said diluent is water.

18. A method as claimed in claim 17 wherein said deflocculation agent is sodium lignosulphonate.

19. A method as claimed in claim 17 or 18 wherein said deflocculation agent/water mixture has been mixed with a sonic mixing procedure.

20. A method as claimed in claim 19 wherein said deflocculation agent/water mixture is added to the mixture of step (iv) substantially at room or ambient temperatures.

21. A method as claimed in any one of the preceding claims wherein the composition comprises -

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Sorbitan Stearate	1.0% w/v
Sodium Lignosulphonate	0.9% w/v
Canola Oil	0.5% w/v
Deionised Water	Up to the 100%.

22. A method as claimed in any one of the preceding claims wherein said mixture includes at least one or more of the following compounds, a trace mineral or trace minerals, synthetic pyrethroid or pyrethroids, an organic phosphate or organo phosphates and closantel sodium.

23. A method as claimed in any one of the preceding claims wherein any such optional trace mineral(s) organo phosphate(s) and/or closantel sodium is mixed into

(a), in the case of trace mineral(s) the pre-mix of step (iv) or (v),

(b), in the case of any organo phosphate(s), in a mix of step (iv) or (v)

(c) in the case of closantel sodium, a mix of step (i),

(d) in the case of pyrantel or morantel, a mix of step (i),

(e) in the case of praziquantel, a mix of step (i), and

(f) in the case of synthetic pyrethroid(s), a mix of step (i).

24. An anthelmintic composition prepared by a method as claimed in any one of the preceding claims.

25. A anthelmintic composition capable of being applied dermally (such as by a pour-on procedure to an animal to deliver a systemicly effective anthelmintic amount of the active ingredient benzimidazole), said composition comprising at room or ambient temperature at least one benzimidazole or prodrug thereof dissolved in, suspended on and/or emulsified by a transdermal vehicle and a liquid carrier for such benzimidazole/vehicle which includes a non-ionic emulsifier, an oil which solubilises the non-ionic emulsifier, water or other diluent, and a deflocculation agent.

26. A composition of claim 25 comprising -

Benzimidazole(s)	1% to 50% w/v,
Transdermal vehicle(s)	2% to 80% w/v,
Non-ionic emulsifier(s)	0.1% to 10% w/v,
Oil(s)	0.1% to 10% w/v,
Deflocculation agent(s)	0.1% to 10%, and
Water or other suitable diluent	5% to 50% w/v.

27. A composition of claim 25 or 26 wherein said benzimidazole or prodrug thereof is selected from the group including oxfendazole, thiabendazole, albendazole, cambenazole, fenbendazole, flubendazole, mebendazole, oxibendazole, parbendazole, thiophanate, febantel, and netobimin,

said vehicle is selected from the group including isopropyl myristate, dimethyl sulphoxide, diacetone alcohol, n-methyl-2-pyrrolidone and 2 pyrrolidone,

said oil is selected from the group including canola oil, polyol fatty acid ester, lauric acid hexyl, oleic acid decyl ester, 2-octyl dodecanol, soybean and sunflower oil, rapeseed, ground nut refined fixed oils.

said non-ionic emulsifier is selected from the group including sorbitan stearate, polysorbates [including ethoxy (20) sorbitan monopalmitate, ethoxy (20) sorbitan monostearate, ethoxy (4) sorbitan monostearate and ethoxy (20) sorbitan tristearate], polyoxyethylene castor oils and polyoxyethylene glycols and

said deflocculation agent is selected from the group including sodium lignosulphonate, silicon dioxides, poly vinyl pyrrolidones.

28. A composition as claimed in any one of claims 25 to 27wherein said benzimidazole is oxfendazole, said vehicle is isopropyl myristate, said oil is canola oil, said non-ionic emulsifier is sorbitan stearate and said deflocculation agent is sodium lignosulphonate.

29. A composition as claimed in any one of claims 25 to 28 which comprises -

Oxfendazole	7.5% w/v
Iso Propyl Myristate	66.0% w/v
Sorbitan Stearate	1.0% w/v
Sodium Lignosulphonate	0.9% w/v

Canola Oil	0.5% w/v
Deionised Water	Up to the 100%.

30. A composition as claimed in any one of claims 24 to 29 which additionally includes at least one trace mineral and/or at least one organo phosphate and/or closantel sodium and/or praziquantel and/or pyrantel, and/or morantel, and/or synthetic pyrethroids.

31. An anthelmintic composition capable by dermal application to an animal of delivering an anthelminticly effective amount of systemic anthelmintic active ingredient into the animal,

systemic anthelmintic compound(s)	1% to 50% w/v,
emulsifier	0.1% to 10% w/v,
carrier solvent (transdermal vehicle)	2% to 80% w/v,
dispersant or wetting agent	0.1% to 10% w/v,
oil	0.1% to 10% w/v, and
diluent	5% to 50% w/v.

32. A composition of claim 31 wherein said anthelmintic compound is a benzimidazole or a prodrug thereof.

33. A method of controlling helminth(s) (nematode, cestode or trematode) within an animal which comprises applying to the skin of the animal composition as claimed in any one of claims 24 to 30, 31 and 32 and thereafter allowing at least the active anthelmintic compound(s) to pass through and/or into the skin of the animal to enter the blood, lymph and/or tissue fluids of the animal in an anthelmintically effective amount.

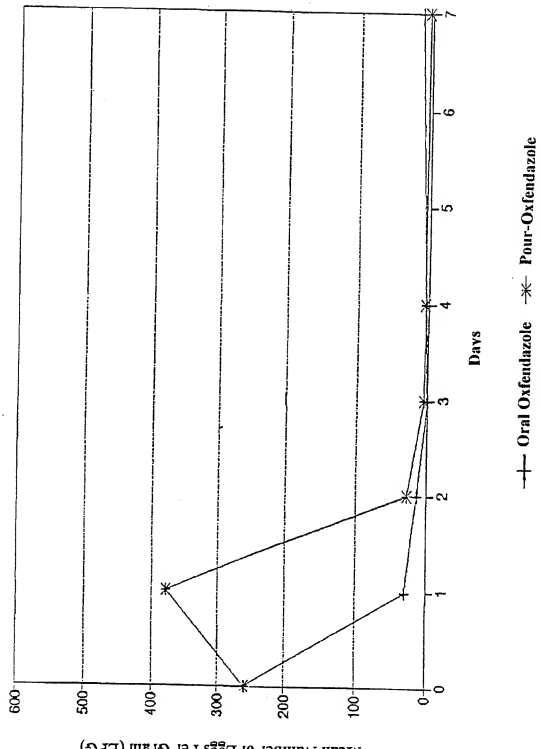
34. A method as claimed in claim 33 wherein said composition is applied by a pour-on procedure.

35. A method of claim 34 wherein said composition is about a 75mg/mL suspension of oxfendazole at about a dosage rate oxfendazole/weight of animal at least twice that recommended for oral administration currently being recommended for oxfendazole anthelmintic treatment of any such animal.

36. A method of claim 34 wherein said composition is about a 75mg/mL suspension of oxfendazole at a dosage rate of about 10mg oxfendazole/kg body weight of the animal.

37. A method of any one of claims 33 to 36 wherein the animal is a ruminant.

FIGURE 1


Mean Number of Eggs Per Gram (EPG)
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
Days
Oral Oxfendazole
Pour-Oxfendazole

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 95/00023

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl.[6] A61K 9/10, 9/107 A01N 25/30 // 31/415, 31/425, 31/215, 31/225 A01N 25/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K KEYWORD SEARCH

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base, and where practicable, search terms used)
DERWENT : WPAT, CASM, KEYWORDS : BENZIMIDAZOLE#, ANTHELMINTIC, ANTI()PARASITIC, ENDOPARASITIC, TROPICAL DERMAL, TRANSDERMAL, EMULS:, SUSPEN:, DRENCH:, POUR()ON

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	AU 10277/92 A1 (HOECHST AKTIENGESELLSCHAFT) 6 August 1992, page 4 line 26 to page 5 line 21, claims.	1-37
X	AU 27505/88 A1 (ANCARE DISTRIBUTORS LIMITED) 20 July 1989, page 3, example 12, claims.	1-37
A	AU 39352/93 A1 (PHARMOS CORP.) 30 September 1993, example 4, claims.	1-37
A	GB 1498816 (FISONS LIMITED) 25 January 1978, whole document.	1-37

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 1995	20 JUNE 1995 (20.06.95)
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION PO BOX 200 WODEN ACT 2606 AUSTRALIA	**DOUGLAS THWAITES**
Facsimile No. 06 2853929	Telephone No. (06) 2832265

C(Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate of the relevant passages	Relevant to Claim No.
A	GB 1464552 (FISONS LIMITED) 16 February 1977, whole document.	1-37
A	GB 1464553 (FISONS LIMITED) 16 February 1977, whole document.	1-37
A	AU 12978/92 A1 (BROCADES PHARMA B.V.) 1 October 1992, examples, claims.	1-37

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member
AU 10277/92	CA 2059602 EP 496316 JP 4312504
AU 27505/88	GB 2213722 NZ 223200
AU 39352/93	WO 9318752
GB 1498816	DE 2537202
GB 1464552	AU 65797/74 JP 50029718 NL 7402438 US 4070476 US 4336262 US 4414222 US 4479960
AU 12978/92	CA 2063862 EP 506197 JP 5262641 NZ 242101

END OF ANNEX